

et al. [8] reported that inflammation is associated with hypoalbuminaemia and increased mortality in HD patients.

These studies and many others suggest that inflammation plays a central role in the development of malnutrition and cardiovascular mortality in patients with chronic kidney disease. On the other hand, more recently, Pupim *et al.* [7] showed that surrogate markers of nutritional status (S-albumin, pre-albumin and serum creatinine) were, indeed, significantly related to all-cause mortality in HD patients, even after adjustment for serum CRP. Although in our study we could not confirm a negative correlation between S-albumin and CRP, taking into account only the baseline measurements, it should be noted that in patients who were persistently inflamed in our study, a negative correlation was, indeed, found between S-albumin and CRP in the four consecutive measurements preceding the study, demonstrating the influence of inflammation on S-albumin levels. We could speculate why this finding could not be verified in the patients who were not persistently inflamed. One reason could be the high prevalence of malnutrition, verified by SGA, in the Brazilian HD population, which differs from American and European HD populations where the majority of earlier studies on these relationships were done. Another reason is that we excluded patients with clinically significant inflammatory events, which in turn could be reflected by the absence of correlation in the whole studied HD population.

In summary, we agree with Tsirpanlis and colleagues that (i) clinically significant inflammatory events modify the levels of S-albumin, (ii) this effect is not immediate and (iii) these factors should be taken into account when analysing the relationship between S-albumin and short acute-phase reactants, such as CRP. We therefore advocate [9] sequential measurements of CRP, which may provide a better approach in the interpretation of decreasing S-albumin levels. On the other hand, it seems reasonable to assume that the S-albumin will remain as a valuable predictor of uraemic malnutrition, inflammation and increased risk for mortality.

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Drug interaction between sevelamer and cyclosporin

This letter was originally published in *NDT* volume 19, issue 7, but without the Reply. The publisher would like to apologise for this error and would now like to publish the paper again to include the Reply.

Sir,

We read with interest the original report made by Miguel-Angel Guillen-Anaya and Michel Jadoul [1] of a drug interaction between sevelamer and cyclosporin (CsA) occurring in a liver transplant patient treated also by chronic haemodialysis. After sevelamer was started, the CsA trough levels reached values as low as 35 ng/ml and they dropped again after rechallenge. As potential explanation, the authors suggest that CsA absorption, which is bile-dependent [2], could be hampered by the fact that sevelamer binds bile acids in the gastrointestinal (GI) tract. Interestingly, in the clinical study performed by Jensen *et al.* [3], the bile-acid sequestrant cholestyramine, 4 g given at noon, did not interfere with CsA absorption.

We would like to mention that sevelamer is a poly(allylaminehydrochloride) polymer that may bind not only phosphate and bile acids, as the authors point out, but also cholesterol, vitamins D, E and K and folic acid [4]. A direct binding of a lipophilic substance such as CsA – and by extension also tacrolimus – appears, therefore, as an additional and more likely explanation.

This observation points to the distinction to be made between the two types of phosphate binding in the GI tract: a specific one achieved by aluminium hydroxide and calcium salts and a non-specific binding attained by polymers such as sevelamer. This absence of specificity might be of less importance for vitamins or folic acid absorption, but may put the patient at risk when lipophilic agents, such as immunosuppressive and/or other drugs (lipophilic statins?), are prescribed. Under those circumstances, it appears that sevelamer should be used with caution, i.e. at least at a time distant of potentially interfering drugs and only when specific (and less expensive) phosphate binders are contraindicated.

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Reply

Sir,
We thank Jean-Pierre Wauters and colleagues for their helpful comments. The lower level of cyclosporin A (CsA) under sevelamer may indeed be due to a direct binding of CsA by sevelamer, rather than to an indirect impact of sevelamer on bile acids. Thus, the recommendation of a delay between the intake of sevelamer and that of drugs such as CsA is fully warranted. We disagree, however, on the claim that calcium-based binding is fully specific for phosphate. Indeed, the co-administration of either calcium acetate or sevelamer with ciprofloxacin recently has been shown to reduce the oral bioavailability of the latter drug by some 50% [1].

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Sevelamer and pharmacokinetics of cyclosporin A after kidney transplantation

Sir,
In their interesting article, Pieper *et al.* analysed prospectively the effect of sevelamer on the pharmacokinetics of cyclosporin (CsA) and mycophenolate mofetil (MMF) in kidney transplanted patients [1]. They provide the reassuring message that, in contrast to MMF, CsA kinetics are not significantly modified by the intake of sevelamer. These results are in sharp contrast to the observation and potential mechanisms that we reported recently [2,3].

The short duration (4 days) and limited statistical power (10 adults and eight children) of the study of Pieper *et al.* make such a strong message rather questionable [4]. Indeed, only 4 days after starting sevelamer, none of the CsA parameters (measured by Cedia and FPIA assays) was completely stable: the area under the curve (AUC) decreased from 3547 ± 660 to 3230 ± 612 ng/h/ml, C_{\max} decreased from 955 ± 193 to 855 ± 272 ng/ml and T_{\max} increased from 1.3 to 1.5 h. In addition, when measured with polyclonal antibodies, the CsA levels decreased significantly and, among its primary metabolites determined by HPLC, the AUC and C_{\max} of AM1—which also has an immunosuppressive action [5]—decreased significantly by 30 and 25%, respectively.

Despite these observations, the authors conclude that 'sevelamer intake for several days does not significantly influence CsA kinetics'. Based on their data, this conclusion appears at least premature, especially if the risk of transplant rejection due to insufficient immunosuppression is considered [6]. Great caution in the use of sevelamer in transplanted patients is still warranted until a careful long-term, large size study on the potential interaction of sevelamer with CsA solves the question.

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